

Claim Listing

Claims 1-25 (previously cancelled)

26. (currently amended) A method for screening identifying organic non-peptide compounds useful in the treatment of cancer, comprising the steps of (1) contacting [[a]] mutant or wild-type mammalian protein of the p53 family [[.]] with an a plurality of organic non-peptide compounds, and (2) measuring determining whether any of said compounds is capable, at a concentration of 1mM or less, of binding to one or more domains of said protein under physiological conditions and restoring or stabilizing a functional conformation therein.

27. (previously presented) The method of claim 26 wherein said protein is human.

28. (previously presented) The method of claim 27 wherein measurement of p53 protein conformation is performed by a method selected from the group consisting of chromatography, spectroscopy, absorption, ultracentrifugation, specific DNA binding assays, and protein binding of another gene product known to be inhibited or activated by p53.

29. (previously presented) The method of claim 27 wherein said protein is a full-length mutant p53 protein.

30. (previously presented) The method of claim 27 wherein the DNA binding domain of said p53 protein is destabilized compared to the wild-type.

31. (previously presented) The method of claim 27 wherein the DNA binding domain of said p53 protein has one or more mutations that render it susceptible to misfolding.

32. (currently amended) The method of claim 27 wherein ~~the DNA binding domain of~~ said p53 protein contains one or more mutations at one or more of residue positions 132, 135, 138, 141, 143 including 143A, 146, 151, 152, 154, 157, 158, 159, 163, 173 including 173A, 176, 179, 186, 194, 196, 213, 220, 237, 238, 241 including 241D, 242, 258, 266, 272, 278, 280, 281, 285, 286, 175 including 175S, 245, 248, 249 including 249S, 273 including 273H, and 282.

33. (previously presented) The method of claim 27 wherein said protein is a p53 deletion derivative.

34. (previously presented) The method of claim 27 wherein said protein comprises the DNA binding domain of said p53 protein without the entire N and C terminal domains.

35. (previously presented) The method of claim 27 wherein the DNA binding domain of said p53 protein is wild-type.

36. (previously presented) The method of claim 27 wherein the DNA binding domain of said p53 protein contains a missense mutation.

37. (previously presented) The method of claim 27 wherein said protein of the p53 family is selected from the group consisting of p53, p63, and p73.

38. (currently amended) The method of claim 27 wherein the contacting and determining measuring steps are performed simultaneously by detecting a conformational change of said p53 protein in the presence of said compound.
39. (previously presented) The method of claim 27 wherein the compound is additionally screened *in vivo* for ability to halt or repress tumor growth.
40. (previously presented) The method of claim 27 further wherein the compound is additionally screened *in vitro* for ability to halt or repress tumor growth.
41. (previously presented) The method of claim 27 wherein said determination is performed using:
- (a) tumor cells that express a mutant of p53 protein; or
 - (b) a cell line that expresses a mutant of p53 protein.
42. (previously presented) The method of claim 27 wherein said mammalian protein of the p53 family is contacted with an organic non-peptide compound at a temperature of approximately 20°C to 50°C.
43. (previously presented) The method of claim 27 comprising anchoring said mammalian protein of the p53 family or said organic non-peptide compound onto a solid phase surface and detecting protein-compound complexes.
44. (previously presented) The method of claim 27 wherein the protein is anchored on a solid support and the compound is labeled.
45. (previously presented) The method of claim 44 wherein the label is a radioisotope or a fluorescent label.
46. (currently amended) The method of claim 27 wherein stabilization of functional p53 protein conformation is ~~determined~~ measured by anchoring said p53 protein, and a detectably-labeled conformationally-sensitive antibody whose binding to an epitope of p53 is dependent upon the presence of native p53 conformation, to a solid support in the presence, and also the absence, of said organic non-peptide compound, and measuring the amount of p53 and/or antibody that is bound to said solid support.
47. (previously presented) The method of claim 27 wherein a monoclonal antibody, specific for p53 DNA binding domain is used to anchor the protein to a solid phase surface.
48. (currently amended) The method of claim 27 wherein said step of measuring determining binding capability and restoration of p53 functional conformation comprises the steps of: (1) contacting the p53 protein with an antibody that specifically recognizes a conformationally sensitive epitope of p53, and (2) determining whether said antibody binds to said protein in the presence of said organic non-peptide compound.
49. (previously presented) The method of claim 48 wherein the presence of epitope correlates with at least one wild-type physiological activity of p53.
50. (previously presented) The method of claim 48 wherein a defect in epitope correlates with at least one inactivated state of p53.

51. (previously presented) The method of claim 48 wherein a detectable label is additionally attached to said antibody by contacting said antibody with a further antibody that is detectably labeled.

52. (previously presented) The method of claim 48 wherein said antibody is mAb 1620 or mAb 240.

53. (previously presented) The method of claim 48 wherein the protein is a temperature sensitive mutant form of p53 possessing an epitope recognized by mAb 240.

54. (previously presented) The method of claim 48 wherein said compound interacts with a protein of the p53 family to restore or stabilize wild-type activity thereof, wherein said activity comprises tumor suppression activity.

55. (currently amended) The method of claim 27 further comprising designing an additional compound that promotes a wild-type activity of a protein of the p53 family wherein said compound is used to generate a hypothesis, identifying a candidate compound that fits the hypothesis, and ~~determining~~ measuring if the candidate compound promotes a wild-type activity of the p53 family.

56. (withdrawn) A method of evaluating whether an organic non-peptide compound can promote a wild-type activity in a mutant form of a mammalian protein of the p53 family, wherein one or more functional activities of said protein are at least partially impaired by the inability of said protein to maintain a functional conformation under physiological conditions, said method comprising the steps of:

- (a) contacting said mutant protein with an organic non-peptide compound that is capable of binding to one or more domains in said mutant protein under physiological conditions and stabilizing a functional conformation therein; and,
- (b₁) permitting said stabilized protein to interact with one or more macromolecules that participate in said wild-type activity with measurement of said activity; or
- (b₂) confirming the presence of said functional conformation via a method selected from the group consisting of chromatography, spectroscopy, absorption, ultracentrifugation, specific DNA binding assays, and protein binding of another gene product known to be inhibited or activated by p53.